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### **Beta-blocker Therapy and Clinical Outcomes in Patients with Moderate COPD and Heightened Cardiovascular Risk**

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## Original Research

### Exacerbations of chronic obstructive pulmonary disease and cardiac events: a cohort analysis

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Performed the primary statistical analyses: BFH, JAA  
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Provided critical input and revised the manuscript for important intellectual content and approved the final manuscript: All  
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## **At a Glance Commentary**

### Scientific Knowledge on the Subject:

- Patients with COPD frequently experience cardiovascular disease (CVD).
- COPD exacerbations are associated with increased systemic inflammation, which is a risk factor for CVD.
- Preliminary data suggest that acute exacerbations of COPD (AECOPD) are associated with an increased risk of subsequent CVD events, but studies have relied on administrative data or non-adjudicated CVD event data.

### What This Study Adds to the Field

- In this **large** cohort of 16,485 COPD patients with CVD or multiple CVD risk factors, exacerbations were followed by an increased risk of adjudicated CVD events, especially in hospitalized COPD patients and in the first 30 days following AECOPD.

## **Abstract**

**Rationale:** Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are common, associated with acute inflammation, and may increase subsequent cardiovascular disease (CVD) risk.

**Objective:** Determine if AECOPD events are associated with increased risk of subsequent CVD.

**Methods:** A secondary cohort analysis of the Study to Understand Mortality and Morbidity (SUMMIT) trial, a convenience sample of current/former smokers with moderate COPD from 1,368 centers in 43 countries. All had CVD or increased CVD risk. AECOPD was defined as an increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids and/or hospitalization. CVD events were a composite outcome of cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack. All CVD events were adjudicated. Cox proportional hazards models compared the hazard for a CVD event prior to AECOPD versus following AECOPD.

### **Measurements and Main Results:**

Among 16,485 participants in SUMMIT, 4,704 participants had at least one AECOPD and 688 had at least one CVD event. The hazard ratio (HR) for CVD events following AECOPD was increased, particularly in the first 30 days following AECOPD (HR 3.8; 95%CI: 2.7 to 5.5) and was elevated up to one year post-AECOPD. The 30-day HR following hospitalized AECOPD was more than two-fold greater (HR 9.9; 95%CI: 6.6 to 14.9).

21 **Conclusions:** In COPD patients with CVD or risk factors for CVD, exacerbations confer an  
22 increased risk of subsequent CVD events, especially in hospitalized patients and within the  
23 first 30 days post-exacerbation. Patients and clinicians should have heightened vigilance for  
24 early CVD events following AECOPD.

25 **Trial Registration:** ClinicalTrials.gov NCT01313676

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27 (NCT01313676, GSK113782). GlaxoSmithKline employees performed the statistical analysis  
28 and participated in the writing group team, but GlaxoSmithKline did not direct or make final  
29 decisions regarding study conception, analysis of results, manuscript writing, or the decision to  
30 submit for publication.

31

32

33 **INTRODUCTION**

34 Ischemic heart disease, stroke, and chronic obstructive pulmonary disease (COPD) are three  
35 leading causes of death globally.<sup>1</sup> These diseases share common risk factors such as older  
36 age and cigarette smoking, yet data suggest that COPD and lower lung function are  
37 independent risk factors for cardiovascular disease (CVD), even after adjustment for traditional  
38 CVD risk factors.<sup>2-4</sup>

39 The mechanisms by which COPD increases CVD risk are not clear, but patients with COPD  
40 often display abnormally high concentrations of circulating systemic inflammatory biomarkers  
41 such as C-reactive protein, interleukin-6, and fibrinogen<sup>5</sup>—biomarkers that predict CVD risk in  
42 the general population<sup>6,7</sup> and in COPD.<sup>8</sup> Acute exacerbations of COPD (AECOPD) are often  
43 associated with particularly high concentrations of these biomarkers<sup>9</sup> which can be slow to  
44 return to baseline.<sup>10</sup>

45 Additionally, many AECOPD events are triggered by infections,<sup>11</sup> and data have shown that  
46 infections (mostly respiratory, but also urinary and gastrointestinal) are associated with an  
47 increased risk for subsequent CVD events.<sup>12-16</sup> The reasons for this are not clear, but  
48 hypotheses have focused on infections as inducers of systemic inflammation and pro-  
49 coagulant pathways that subsequently lead to cardiovascular events.

50 Two previous studies have suggested that AECOPD increases risk for subsequent CVD, but  
51 both had significant methodologic limitations including use of administrative data to define  
52 COPD, AECOPD and CVD events<sup>17</sup> or use of non-adjudicated adverse event reporting data.<sup>18</sup>

53 The Study to Understand Mortality and MorbidITy (SUMMIT) trial was an international,  
54 multicenter trial of patients with COPD and either a history of CVD or heightened risk for CVD.  
55 SUMMIT assessed the impact of inhaler treatments on mortality and rigorously adjudicated  
56 CVD events, therefore reducing the risk of ascertainment bias and providing more accurate  
57 estimates of risk. We hypothesized that time periods following AECOPD would be associated  
58 with higher risk for CVD events compared with time periods free of AECOPD.

59 **Some of the results of this study have been previously reported in the form of an abstract.<sup>19</sup>**

## 60 **METHODS**

61 A detailed description of our methods is included with the **Online Supplement**. In brief, we  
62 performed a post-hoc cohort analysis using data in SUMMIT, a double-blind, parallel group,  
63 placebo-controlled, randomized trial conducted at 1,368 centers in 43 countries between 2011  
64 and 2015. Details of the study design and main results are published.<sup>20,21</sup> Participants  
65 (n=16,485) were randomly assigned to receive either inhaled placebo, fluticasone furoate,  
66 vilanterol, or the combination of fluticasone furoate and vilanterol. The study showed no  
67 significant differences in risk of death or cardiovascular events between the four arms of the  
68 trial.

69 Participants were current or former smokers with at least a 10-pack-year smoking history, aged  
70 40–80 years with a ratio of forced expiratory volume in 1 s to forced vital capacity (FEV<sub>1</sub>/FVC)  
71 ≤70%, FEV<sub>1</sub> 50%-70% of predicted, and a modified Medical Research Council dyspnea scale  
72 score of ≥2. Participants 40-59 years old were required to have a history of CVD, defined as  
73 coronary artery disease, peripheral arterial disease, stroke, myocardial infarction, or diabetes



74 mellitus with target organ disease. Participants 60-80 years old could have either a history of  
75 CVD or increased risk for CVD, defined as receiving medication for two or more of the  
76 following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease.

77 Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery,  
78 receiving long-term oxygen, chronic oral corticosteroid therapy, severe heart failure (New York  
79 Heart Association Class IV or ejection fraction <30%), life expectancy less than three years,  
80 and end-stage chronic renal disease.

81 Participants were seen every three months at which time data relating to AECOPD and CVD  
82 were assessed.

### 83 Statistical analysis

84 We used Cox proportional hazards models with time-dependent 'period' covariates, where the  
85 hazard for a CVD event was compared between the period prior to AECOPD ('baseline' in our  
86 tables) and following AECOPD (**Online Supplement Figure S1**). AECOPD was defined as an  
87 increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids  
88 and/or hospitalization. Our primary outcome was a composite CVD outcome that included  
89 cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic  
90 attack. A clinical endpoint committee (CEC) **used data from medical records, witness**  
91 **interviews, autopsy reports, and death certificates to** adjudicated all CVD events using  
92 **standardized guidelines.**<sup>22,23</sup> ~~medical records, witness interviews, autopsy reports, and death~~  
93 ~~certificates.~~

94 We excluded events where AECOPD and CVD were reported on the same day, as we were  
95 unable to determine which event happened first. We analyzed the hazard of post-AECOPD  
96 CVD events at 1-30 days, 31-90 days, 91 days-1 year, and >1 year following AECOPD events.  
97 Covariates are detailed in our table legends. In cases where participants experienced more  
98 than one AECOPD, only the first was used. Data were censored after the first CVD event.

99 Secondary analyses focused on: 1) only hospitalized AECOPDs, 2) only myocardial  
100 infarctions, 3) comparison of those with established CVD versus those with only increased  
101 CVD risk, 4) restriction to each of the four arms of the trial, and 5) restriction to only those who  
102 experienced an AECOPD event during the study.

103

## 104 **RESULTS**

105 Among the 16,485 participants in SUMMIT, 75% were male, 47% were current smokers, mean  
106 body mass index (BMI) was 28 kg/m<sup>2</sup> and 39% had a history of one or more AECOPD events  
107 in the year prior to enrolment (**Table 1**).

108 Median participant on-treatment follow up time was 1.5 years with a total of 26,946 patient  
109 years of follow-up. During follow-up, 4,704 participants had at least one AECOPD and 688 had  
110 at least one adjudicated CVD event. The first CVD event was CV death in 271, myocardial  
111 infarction in 173, stroke in 127, unstable angina in 83, and transient ischemic attack in 34.

112 Depending on the particular analysis, between 0 to 9 participants were excluded due to  
113 reporting CVD and AECOPD on the same day.

114 A total of 487 participants experienced a CVD event during the baseline period (487 events in  
115 21,624 patient years is 2.3 per 100 patient-years). Between days 1 to 30 following AECOPD,  
116 32 participants experienced a CVD event (8.8 per 100 patient-years); 29 participants had a  
117 CVD event between days 31 to 90 (4.4 per 100 patient-years); 91 participants had a CVD  
118 event between day 91 to 1 year (4.0 per 100 patient-years) and 41 participants had a CVD  
119 event after 1 year (2.4 per 100 patient-years). Compared with pre-AECOPD baseline periods,  
120 the hazard of CVD events following AECOPD was increased, particularly in the first 30 days  
121 following AECOPD (HR 3.8; 95%CI: 2.7 to 5.5), though it remained increased between 31  
122 days - 90 days and 91 days - 1 year, and was no longer increased beyond 1 year following  
123 AECOPD (**Table 2** and **Figure 1-2**).

124 In a further analysis, we restricted the AECOPD events to only hospitalized AECOPD events  
125 and considered participants who had a non-hospitalized AECOPD to remain in the baseline  
126 period. A total of 605 participants experienced a CVD event during the baseline period (2.4 per  
127 100 patient-years). Between days 1 to 30 following hospitalized AECOPD, 24 participants  
128 experienced a CVD event (26.7 per 100 patient-years); 15 participants had a CVD event  
129 between days 31 to 90 (9.9 per 100 patient-years); 24 participants had a CVD event between  
130 day 91 to 1 year (4.9 per 100 patient-years) and 11 participants had a CVD event after 1 year  
131 (3.3 per 100 patient-years). In this case, the post-AECOPD hazard for CVD events was again  
132 particularly increased in the first 30 days following hospitalized AECOPD (HR 9.9; 95%CI: 6.6

133 to 14.9), remained increased between 31 days - 90 days and 91 days - 1 year, but was not  
134 increased beyond one year following hospitalized AECOPD (**Table 2** and **Figure 1 2**).

135 Analyses restricted only to those who experienced an AECOPD event during the study  
136 (n=4,629 with all covariates) showed that the hazard for CVD following AECOPD was again  
137 particularly increased in the first 30 days following AECOPD (HR 6.4; 95% CI: 4.1 to 10.2). The  
138 hazard was attenuated, but still significant, between 31 days - 1 year following AECOPD, and  
139 remained slightly elevated >1 year after AECOPD (**Table 3**).

140 Analyses restricted to only myocardial infarction events (i.e., excluding other non-myocardial  
141 infarction CVD events) showed similar results, with a substantially increased risk of myocardial  
142 infarction in the first 30 days following AECOPD, a lower, but still significant, risk between 31  
143 days - 1 year, and no significant increased risk beyond 1 year (**Online Supplement, Table**  
144 **S1**).

145 Analyses stratified by whether participants entered the study with a history of established CVD  
146 or CVD risk are shown in **Online Supplement, Table S2**. The hazard ratio for experiencing a  
147 CVD event following AECOPD was again most pronounced in the first 30 days following  
148 AECOPD, regardless of whether participants entered the study with established CVD or CVD  
149 risk. Among those with established CVD, the younger and older age groups had similar 95%  
150 CI bounds for the hazard ratios at each time period post-AECOPD, but there were very few  
151 CVD events, so these estimates may not be reliable.

152 Lastly, we analyzed the hazard for CVD following AECOPD separately in each of the four  
153 original trial arms of the parent SUMMIT study. Results were again similar to that observed in  
154 our other analyses, with each arm demonstrating hazard ratios that were particularly increased  
155 in the first 30 days following AECOPD, remained increased between 31 days - 1 year, and  
156 were no longer significant beyond 1 year following AECOPD (**Online Supplement, Table S3**).

157

## 158 **DISCUSSION**

159 This analysis of prospectively collected data from a multi-center, international study of patients  
160 with moderately severe COPD and rigorously adjudicated CVD events supports the notion that  
161 AECOPD increases the risk for subsequent CVD events, especially in the first 30 days  
162 following an AECOPD. Moreover, the observed effect size was substantial, with a 4-fold  
163 increased hazard for CVD events following AECOPD, and a 10-fold increase in those  
164 hospitalized with AECOPD. These results suggest that clinicians and patients need to be  
165 vigilant for the occurrence of CVD events following AECOPD, especially in those hospitalized  
166 with AECOPD.

167 Our findings are notable for remarkable consistency among the primary analysis and the  
168 multiple secondary analyses regarding the particularly high CVD risk in the first 30 days  
169 following AECOPD, whether we analyzed all AECOPD events, hospitalized AECOPD events,  
170 myocardial infarctions only, or stratified by age and established CVD versus CVD risk. Our  
171 sample of over 16,000 study participants ~~is one of the largest prospective COPD studies~~

172 ~~conducted to date and the multi-center, multi-national design~~ **enrolled from multiples sites**  
173 **and countries** increases the generalizability to patients seen in varying clinical settings. Our  
174 findings are further strengthened by the blinded adjudication of CVD events. This adjudication  
175 provides us with a high degree of confidence regarding the validity of the CVD events.

176 Our findings validate preliminary observations in the Understanding Potential Long-term  
177 Impacts on Function with Tiotropium (UPLIFT) trial, where AECOPD was associated with a  
178 higher risk of cardiovascular SAEs in both the first 30 and first 180 days post-AECOPD, with  
179 higher risk in the first 30 days.<sup>18</sup> CVD event data in UPLIFT consisted of only serious adverse  
180 event (SAE) reporting data without detailed adjudication, and the analysis did not include  
181 adjustment for multiple potential confounders. Unlike SUMMIT, UPLIFT did not specifically  
182 select for COPD patients at risk for CVD, but in both UPLIFT and our SUMMIT results,  
183 associations between AECOPD and CVD were present whether patients entered the studies  
184 with a history of previously diagnosed CVD or not.

185 Our findings also build upon a previous study of AECOPD and CVD relationships using  
186 administrative data in England and Wales. Among those with administrative codes for  
187 physician-diagnosed COPD (not necessarily confirmed by spirometry), prescriptions for oral  
188 antibiotics and corticosteroids (considered a surrogate marker of AECOPD) were associated  
189 with a higher risk for subsequent myocardial infarctions and stroke.<sup>17</sup> These associations were  
190 dependent on the outcomes and time-period examined. For example, the increased risk for  
191 myocardial infarction was only observed for five days following a prescription for both  
192 antibiotics and steroids—there was no association with antibiotics alone, steroids alone, or  
193 beyond five days of the combination prescription. However, for stroke, the association was

194 significant up to 49 days after a prescription for a steroid or an antibiotic, but not the  
195 combination steroid plus antibiotic. These complex observations may reflect the limitations of  
196 administrative data, as compared with our study's strict criteria for spirometry confirmation of  
197 COPD, prospective collection of pre-defined AECOPD and CVD data, and detailed  
198 adjudication of CVD events.

199 AECOPD events are associated with elevated concentrations of circulating pro-inflammatory  
200 biomarkers<sup>24</sup> that can be slow to return to baseline.<sup>10</sup> The high initial concentrations with slow  
201 recovery might help explain why we observed the most risk for CVD in the first 30 days post-  
202 AECOPD, but we continued to observe a statistically significant, albeit much smaller, risk up to  
203 one year post-AECOPD. The prolonged duration of increased CVD risk is consistent with  
204 studies that have shown that respiratory events such as pneumonia<sup>13</sup> and other respiratory  
205 infections<sup>14</sup> are associated with prolonged CVD risk.

206 Inflammation might also explain why hospitalized AECOPD patients had a 30-day CVD risk  
207 more than double that seen in those with less severe AECOPD. Hospitalized AECOPD  
208 episodes are often associated with higher concentrations of circulating pro-inflammatory  
209 biomarkers compared to AECOPD events treated outside of the hospital.<sup>25</sup> We did not  
210 measure biomarkers in this study, so we were unable to determine the contribution of  
211 inflammation to post-AECOPD CVD risk. We were also unable to test other potential  
212 mechanisms such as AECOPD leading to hypoxemia, increased respiratory muscle work  
213 diverting perfusion from the coronary circulation, induction of a pro-thrombotic state, increases  
214 in blood pressure, or worsening adherence to non-respiratory medications.

215 From a therapeutic standpoint, our data suggest that the immediate post-AECOPD period is a  
216 window of heightened CVD susceptibility, and therefore future studies should test interventions  
217 in this period to reduce CVD risk. Possible interventions to test might include established CVD  
218 therapies (e.g. antiplatelet agents, statins, and/or beta blockers) and/or experimental CVD  
219 interventions (e.g. anti-inflammatory drugs).

220 Our study has several important limitations. SUMMIT participants were selected based on  
221 being at high CVD risk either due to pre-existing disease or having multiple risk factors for  
222 CVD. Although estimates of CVD prevalence in patients with COPD have ranged from 28% to  
223 70%,<sup>3</sup> our findings may not apply to COPD patients without CVD or CVD risk factors. SUMMIT  
224 participation was also restricted to those with FEV<sub>1</sub> between 50%-70% of predicted, so we  
225 cannot generalize our findings to those with milder or more severe airflow limitation. Our  
226 follow-up time was also relatively short, at a median of 1.5 years. While data from our study  
227 and other studies suggest that most of the excess CVD risk occurs within the first year after  
228 AECOPD, we had limited power to study long-term event risk beyond one year. Lastly,  
229 although CVD events were adjudicated, AECOPD events were self-reported and not  
230 adjudicated. **Therefore, we cannot exclude the possibility that some AECOPD events**  
231 **were CVD events to begin with.** However, our AECOPD definition is that used by nearly  
232 every contemporary COPD trial and is a definition that has proven to be modifiable by  
233 treatments such as inhalers and oral medications.<sup>26</sup> Moreover, we found even stronger  
234 associations in hospitalized patients who ~~have presumably had~~ **typically undergo** more  
235 detailed assessments for other clinical etiologies of acute-onset dyspnea (e.g. pneumonia,  
236 myocardial infarction, pulmonary embolism) compared to outpatients. Therefore, we think  
237 misclassification of AECOPD is not likely.



238

239 **CONCLUSION**

240 In COPD patients with CVD or risk factors for CVD, exacerbations confer an increased risk of  
241 subsequent CVD events, especially in hospitalized patients and within the first 30 days post-  
242 exacerbation. Patients and clinicians should have heightened vigilance for early CVD events in  
243 this patient group following AECOPD.

244

245

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248

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251

252 Declaration of interests:

253 MTD has received consultancy fees from GlaxoSmithKline, AstraZeneca, Boehringer  
254 Ingelheim, and Genentech, and has received research support from GlaxoSmithKline,  
255 AstraZeneca, Boehringer Ingelheim, Novartis, Yungjin, PneumRx, Pulmonx, and Mereo.

256 RDB has received consultancy fees from GlaxoSmithKline.

257 PMAC has advised Boehringer Ingelheim, GSK, AstraZeneca and Takeda on the design and  
258 conduct of clinical trials and has spoken at meetings sponsored by these companies and by  
259 Novartis.

260 BRC has received consultancy fees from GlaxoSmithKline, is a board/advisory committee  
261 member for GlaxoSmithKline, AstraZeneca, and Boehringer Ingelheim, and has received  
262 research support from AstraZeneca.

263 FJM has received consultancy fees from Axon Communication, Johnson & Johnson, Bioscale,  
264 and Unity Biotechnology, is a board/advisory committee member for Bayer, Boehringer

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271 WebMD, and PeerView Network; and publication royalties from Informa.

272 DENewby has received consultancy fees from GlaxoSmithKline, is a board/advisory committee  
273 member for GlaxoSmithKline, has received speaker fees from GlaxoSmithKline, and has  
274 received research support from GlaxoSmithKline

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276 Boehringer Ingelheim, and Novartis.

277 JAA, CC, and JCY are employees of GlaxoSmithKline and hold shares in the company.

278 DENiewoehner has received consultancy fees from GlaxoSmithKline, Boehringer Ingelheim,  
279 and Forrest Research.

280 BH was a previous employee of GlaxoSmithKline, holds shares in the company and is an  
281 employee of Veramed who are contracted to perform statistical analyses for GlaxoSmithKline.

282 KMK and AAP declare no conflicts of interest.

283

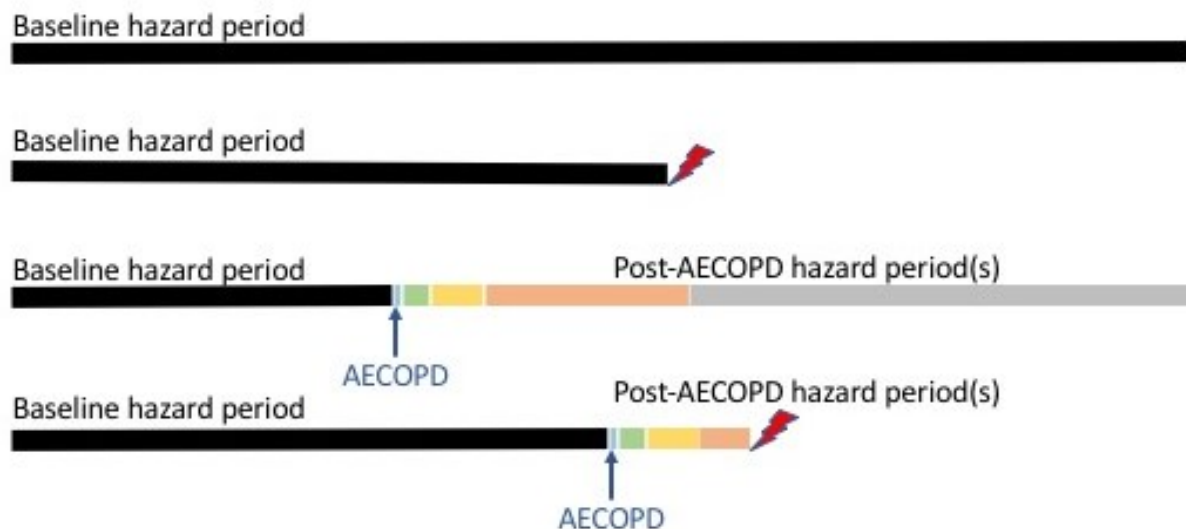
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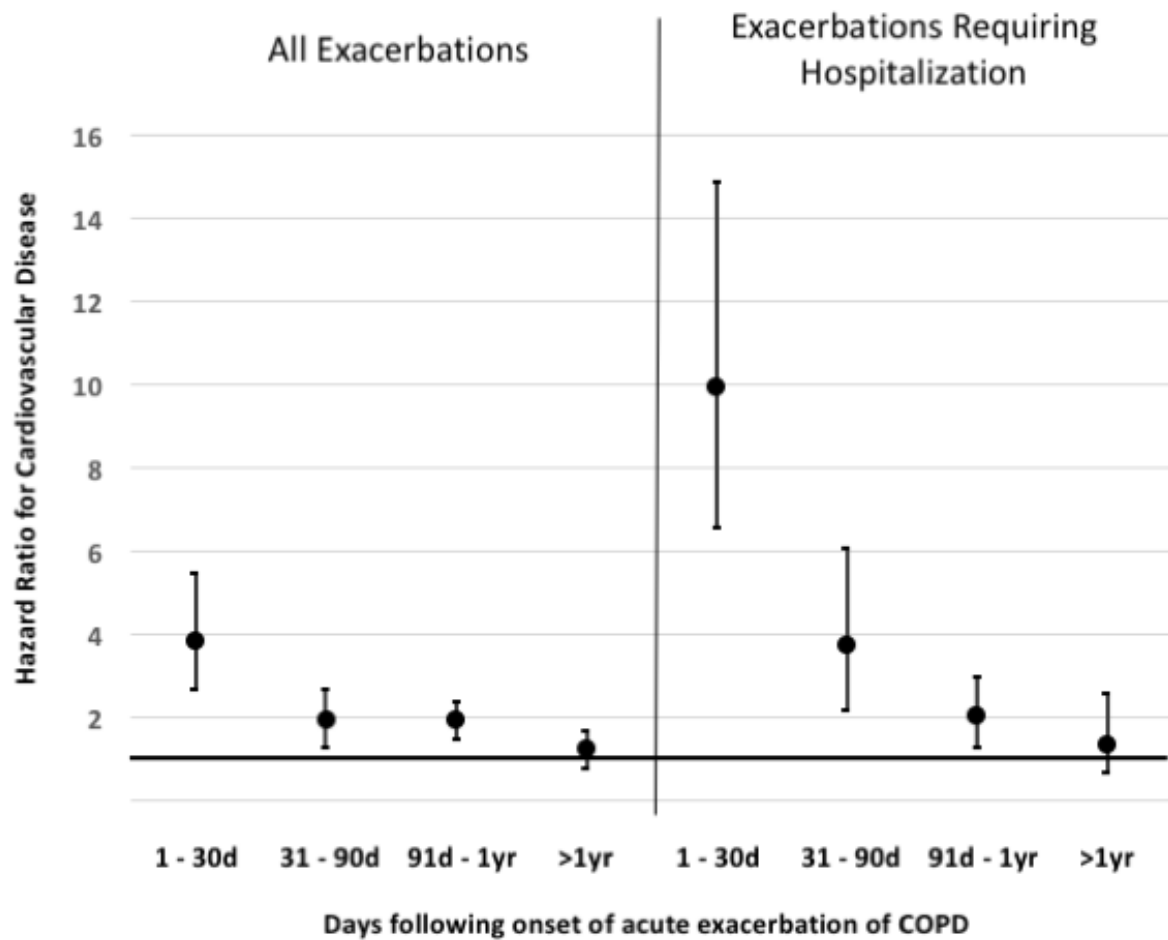
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**Figure 1.** Graphical representation of analytic method. All study participants with any follow-up time contribute to the analysis. Participants can have one of four possible patterns, as graphically shown below, from the top down: 1) No acute exacerbation of chronic obstructive pulmonary disease [AECOPD] (black bars) and no cardiovascular disease [CVD] events (as depicted by red bolts), 2) No AECOPD, but with CVD event, 3) AECOPD (as indicated by blue arrow/bar), but with no CVD event, and 4) AECOPD and CVD event. All participants with any follow-up time contribute to baseline hazard data for CVD events. Participants with AECOPD events contribute baseline hazard data for both baseline, exacerbation-free periods (black bars) and comparison data regarding post-AECOPD hazard data at 1-30 days after AECOPD (green bars), 31-90 days after AECOPD (yellow bars), 91 days-1 year after AECOPD (orange bars) and >1 year after AECOPD (grey bars). Data are censored at the time of a CVD event. Secondary analyses included: 1) only hospitalized AECOPD events, where participants who had a non-hospitalized AECOPD remained in the baseline period ([Table 2](#)), and 2) restriction to only the last two groups who experienced an AECOPD during the study ([Table 3](#)).



**Figure 1.2.** Hazard ratios (95% confidence intervals) for cardiovascular disease (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) following an acute exacerbation of chronic obstructive pulmonary disease.





**Table 1.** Study participant characteristics. Reported as mean (SD) or n (%).

	<b>Total (n = 16,485)</b>
Age (years)	65 (8)
Female	4,196 (25%)
Race	
White	13,357 (81%)
Asian	2,724 (17%)
Other	404 (2%)
Body mass index (kg/m <sup>2</sup> )	28 (6)
Current Smokers	7,678 (47%)
Smoking History (pack-years)	41 (24)
Systolic blood pressure, mmHg	135 (15)
Diastolic blood pressure, mmHg	80 (10)
Cardiac comorbidities	
Coronary artery disease	8,379 (51%)
Previous myocardial infarction	2,774 (17%)
Previous stroke	1,595 (10%)
Hypercholesterolemia	11,518 (70%)
Hypertension	14,851 (90%)
Diabetes mellitus	4,997 (30%)
Cardiac medications	
Antiplatelet	8,517 (52%)
Statin	10,721 (65%)
Beta-blocker	5,667 (34%)

Diuretic	6,148 (37%)
Post-Bronchodilator FEV <sub>1</sub> (L)	1.70 (0.40)
% Predicted post-bronchodilator FEV <sub>1</sub>	59.7 (6.1)
Pre-study COPD inhaler therapy	
Long-acting $\beta$ -agonist	5,769 (35%)
Long-acting muscarinic antagonist	2,550 (15%)
Inhaled corticosteroid	5,486 (33%)
Pre-study exacerbations in 12 months before study	
0	10,021 (61%)
1	4,020 (24%)
2+	2,444 (15%)

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV<sub>1</sub>=forced expiratory volume in 1 second.

**Table 2.** Hazard ratios for cardiovascular disease (CVD) event (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Analysis shown for all exacerbations (top) and for exacerbations requiring hospitalization (bottom).

Period	Number of Participants in Period	Observed Follow-up in Period (Patient-Years)	Number of Participants with adjudicated CVD event	Hazard Ratio (95% CI)
<b>All Exacerbations</b>				
Baseline, AECOPD-free	16,477	21,624	487	-reference-
1 – 30 days	4,639	363	32	3.8 (2.7 to 5.5)
31 days – 90 days	4,235	658	29	1.9 (1.3 to 2.7)
91 days – 1 year	3,779	2,267	91	1.9 (1.5 to 2.4)
>1 year	2,179	1,744	41	1.2 (0.8 to 1.7)
<b>Exacerbations Requiring Hospitalization</b>				
Baseline, AECOPD-free	16,476	25,595	605	-reference-
1 – 30 days	1,243	90	24	9.9 (6.6 to 14.9)
31 – 90 days	998	152	15	3.7 (2.2 to 6.1)
91 days – 1 year	862	487	24	2.0 (1.3 to 3.0)
>1 year	447	330	11	1.3 (0.7 to 2.6)

Covariates included: AECOPD period (baseline free of AECOPD or other post-AECOPD periods as in Figure 1), treatment assignment arm, age, sex, body mass index (BMI), region, race, ethnicity, ischemic and vascular indicators (e.g. previous treatment of coronary or vascular disease), cardiovascular disease/risk indicators (with CVD; with CV risk), smoking status, previous exacerbation history, and percent predicted post-bronchodilator FEV<sub>1</sub>

8 participants were excluded from the 'All Exacerbations' analysis due to experiencing an AECOPD and CVD event on the same day; 9 were excluded from the 'Exacerbations Requiring Hospitalization' analysis due to experiencing an AECOPD and CVD event on the same day. 183 participants were excluded from the calculation of the Hazard Ratios in both analyses because they did not have all model covariates.

**Table 3.** Secondary analysis restricted to only those study participants who experienced an AECOPD event during the study. Hazard ratios for CVD events following an AECOPD. Due to small numbers in this restricted analysis, the post-AECOPD periods of 31-90 days and 90 days-1 year were combined.

Period	Number of Participants in Period	Observed Follow-up in Period (Patient-Years)	Number of Participants with adjudicated CVD event	Hazard Ratio (95% CI)
Baseline, AECOPD-free	4,696	3,695	55	<i>-reference-</i>
1 – 30 days	4,639	363	32	6.4 (4.1 to 10.2)
31 days – 1 year	4,235	2,926	120	3.0 (2.1 to 4.4)
>1 year	2,179	1,744	41	1.8 (1.1 to 3.1)

Covariates included: AECOPD period (baseline free of AECOPD or other post-AECOPD periods as in Figure 1), treatment assignment arm, age, sex, body mass index (BMI), region, race, ethnicity, ischemic and vascular indicators (e.g. previous treatment of coronary or vascular disease), cardiovascular disease/risk indicators (with CVD; with CV risk), smoking status, previous exacerbation history, and percent predicted post-bronchodilator FEV<sub>1</sub>

8 participants were excluded due to experiencing an AECOPD and CVD event on the same day. 67 participants were excluded from the calculation of the Hazard Ratios because they did not have all model covariates.